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SUPPRESSION BY 1,3-BUTANEDIOL OF THE ETHANOL WITHDRAWAL SYNDROM--ETC(U)
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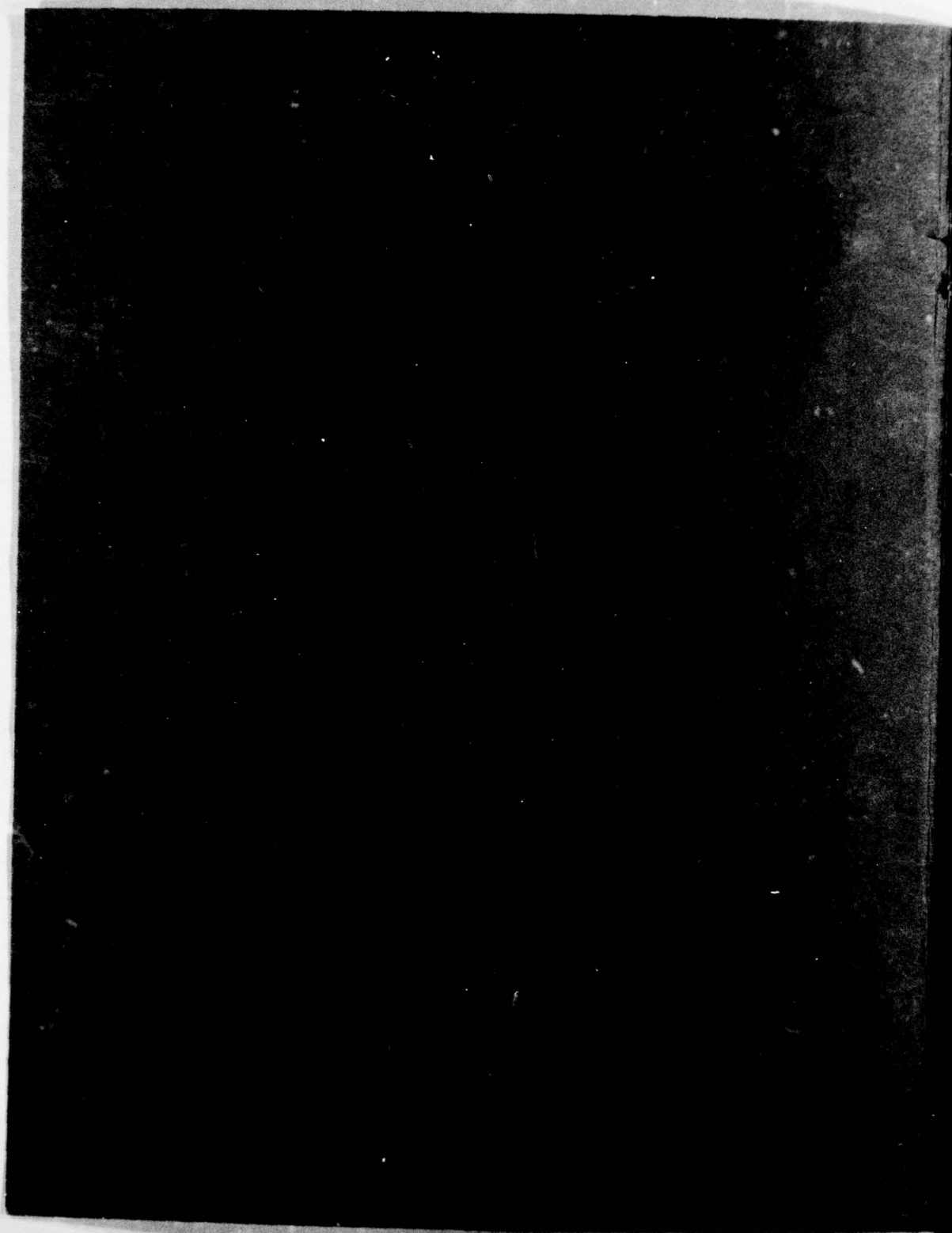
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) 1,3-Butanediol (BD) was tested for its ability to suppress an ethanol withdrawal syndrome. Male Sprague-Dawley rats were rendered physically dependent upon ethanol by intragastric administration of 9-15 g/kg of ethanol per day over a 4-day period. A nonintoxicating dose of BD of 4 g/kg, p.o., administered after elimination of ethanol from the blood was effective against the tremulous and convulsive components in all animals for 1-5 hours. This period of time coincided with the time of		

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20. **ABSTRACT (continued)**

maximum severity of the withdrawal syndrome as seen in the control animals. These results suggest that BD may be useful in the treatment of the ethanol withdrawal syndrome in man.

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PREFACE

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INTRODUCTION

The clinical management of ethanol withdrawal has to consider both acute and chronic aspects of ethanol intake. During the early stages of the withdrawal period, a subject displays signs of intoxication similar to those observed during the first drinking episode. As detoxication proceeds and the blood ethanol concentrations decline to approximately 100 mg/dl, a gradual transition develops from depression to hyperexcitability. With the total elimination of blood ethanol, a series of neurological signs and reactions emerge which include general agitation, tremors, convulsions, hallucinations and delirium tremens.^{11,24,32} In addition, a number of side effects resulting from long-term intoxication with heavy doses of ethanol are evident. These may include malnutrition, weight loss, a lessened resistance to infection, hepatitis, cirrhosis of the liver, various vitamin deficiencies, peripheral neuropathy and general, neurological, psychiatric and clinical deterioration.^{11,24,32} Thus, an ethanol withdrawal syndrome can be a serious medical problem and may be fatal if not properly managed. Therefore, the primary aim of treatment is to reduce the neuromuscular and autonomic hyperactivity, thereby preventing exhaustion so that necessary clinical management and treatment can proceed.³²

Empirically, any drug that will suppress nervous excitability may ameliorate the severity of the withdrawal reaction. To date a variety of compounds which are either structurally or pharmacologically similar to ethanol have been effective in treatment.³¹ Among these have included aliphatic alcohols and their corresponding aldehydes, paraldehyde, chloral hydrate, barbiturates, phenothiazines, and benzodiazepines.³¹ However, the optimal drug is not only efficacious in controlling the withdrawal syndrome, but is devoid of major side effects. Of the drugs just listed, some are either more toxic than ethanol or have severe side effects including their ability to induce dependence.^{1,13,31}

The availability of a number of animal models of ethanol dependence^{5,6,8-10,15,16,22,23,26,27,29,33,34} now allows the testing of a variety of potential chemotherapeutic agents for their ability to suppress the signs and

responses of the ethanol withdrawal syndrome. Utilizing the model of ethanol dependence in the rat recently developed in this laboratory,¹⁸⁻²⁰ a number of compounds were screened and found to be effective. Of these, 1,3-butanediol (BD), a compound of low toxicity^{2-4,7,25} suppresses a variety of signs and responses in rats characteristic of the ethanol withdrawal syndrome.

METHODS

Male Sprague-Dawley rats (200-300 g) (Caw:CFE(SD)) were rendered ethanol-dependent by intubation of a 20 percent solution of ethanol at 9-15 g/kg daily in up to six fractions over a 4-day period.¹⁸⁻²⁰ Since for the induction of ethanol dependence the maximum tolerable doses were used, about one-third of the animals usually died due to overdosage. On the day of withdrawal, the animals were observed at hourly intervals, initially for the disappearance of ethanol intoxication and then for the onset of an ethanol withdrawal syndrome. Blood samples were taken also at hourly intervals from the tail vein but starting with the onset of signs of the ethanol withdrawal syndrome. This continued until the complete clearance of ethanol from the blood. Blood ethanol levels were determined using an automated adaptation¹⁷ of a gas chromatographic method of Roach and Creaven.²⁸ At this point the animals were treated with BD (4 g/kg, p.o.) or untreated. The group to which a given animal was assigned was determined using a table of random numbers on a single blind basis, i.e., the experimenter doing the behavioral evaluations was unaware of which animals were treated with BD. Hourly evaluations continued until the disappearance of the overt signs of the withdrawal syndrome (Figure 1).

The onset of the withdrawal syndrome was based on visual and tactile evaluation of the intensity of the following signs: tremors of the tail, caudal region and head, general tremors, tail rigidity, general rigidity, hyperactivity and convulsions. For the scoring of BD's effectiveness in suppressing the withdrawal syndrome only the tremors were used. These were rated on a scale of 1, 2, or 3 and were classified into mild, moderate, and severe, respectively.¹⁸⁻²⁰ In general, the severity of tremors of the tail and caudal region

ranged from 1-3, whereas the maximum score of the head tremors usually was not higher than 2. The severity of the withdrawal is expressed as a total score which represents the sum of the individual scores assessed for four types of tremors observed at each observation session.

RESULTS

The withdrawal tremors usually lasted from 20-24 hours in animals that received no treatment (Figure 1). This period corresponds to the time from the onset of the withdrawal when ethanol was still present in the blood to the total disappearance of the overt signs and responses of the withdrawal syndrome. However, the period of withdrawal corresponding to the time when ethanol was

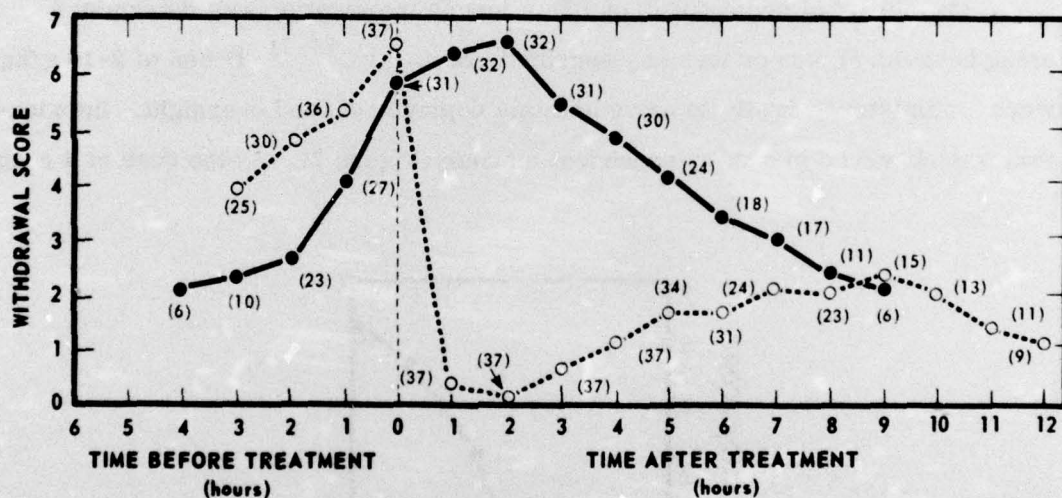


Figure 1. Effect of 1,3-butanediol (BD) (4 g/kg, p.o.) on the withdrawal score. The withdrawal score is defined in the text. ●—● refers to untreated ethanol-dependent rats. o----o refers to BD-treated, ethanol-dependent rats. Time zero corresponds to the point at which all ethanol has been eliminated from the blood, and for BD-treated animals denotes the point at which BD was administered. Numbers in parentheses denote the number of animals observed, while each point refers to the mean of the withdrawal scores. Statistical differences were found for the period 1-5 hours after BD treatment using the median test ($P < 0.05$).

still present in the blood was 4-6 hours. The maximum severity of the withdrawal reactions usually occurred when blood ethanol levels decreased to less than 100 mg/dl and up to 4 hours later.

Administration of single doses of BD reduced the severity of the withdrawal tremors for varying periods of time in different animals. In general, the score dropped to about zero in all treated animals and was statistically different from controls for 1-5 hours when compared using the median test ($P < 0.05$) (Figure 1). This period also coincided with the time of maximum severity of the withdrawal syndrome as seen in the controls. The tremors reappeared with a severity and time course of recovery similar to the untreated animals approximately 8 hours after administration of BD. Additionally, no convulsions were observed in any of the BD-treated animals.

The ability of acute doses of BD to induce intoxication was determined using behavioral parameters as described previously.¹⁸⁻²¹ Doses of 2-10 g/kg were administered orally to naive animals deprived of food overnight. Intoxication was observed in a dose-dependent manner (Figure 2). At the dose of 4 g/kg

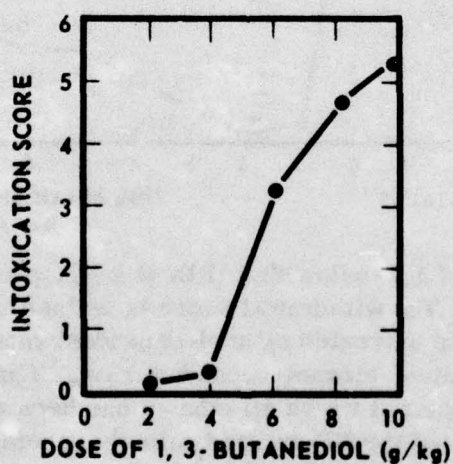


Figure 2. Effect of 1,3-butanediol on naive rats. Each group contained four animals. The intoxication score was assigned as follows: 0 - normal; 1 - sedation; 2 - ataxia 1; 3 - ataxia 2; 4 - ataxia 3; 5 - loss of righting reflex; 6 - coma.¹⁸⁻²⁰

used for suppressing the ethanol withdrawal syndrome, no significant degree of intoxication was observed.

DISCUSSION

The results reported here indicate that BD effectively suppresses the tremulous and convulsive components of the ethanol withdrawal syndrome in the rat. This would suggest the possible use of this compound in treatment of some aspects of the human counterpart. Although serious consideration of clinical application is premature, BD has a number of positive attributes. In addition to being able to ameliorate withdrawal signs, it is nonintoxicating in the doses used (Figure 2).¹⁴ Some of its pharmacological and biological properties have been established during the last 30 years in studies using BD as a synthetic source of calories.³⁰ In general, BD is relatively nontoxic in both humans¹² and experimental animals,^{2-4,7,14,25} and has little or no toxic effects with doses used in this study. There have been no reports suggesting that long-term consumption of BD can induce physical dependence or intoxication. However, since in our experiment highly intoxicating amounts of ethanol are necessary to induce physical dependence, the possibility that BD could be addictive cannot be excluded.

Whether BD can be used in a clinical setting remains to be determined. Also, because of its structural similarity to ethanol, BD and other related compounds may be useful in exploring the specificity of alcohols in inducing physical dependence.

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